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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,249	06/23/2006	Tomoyoshi Ishikawa	081356-0261	1542

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EXAMINER	
KIM, YUNSOO	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,249	ISHIKAWA ET AL.	
	Examiner	Art Unit	
	YUNSOO KIM	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,9-14,18 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7,9-14,18 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/09 has been entered.

2. Claims 1, 2, 4, 7, 9-14, 18 and 21 are pending and are under consideration in the instant application.

3. The declaration of Eiji Sawa under 37. C.F.R. 1.132 filed on 11/9/09 has been considered.

The declaration states that the use of glutamate unexpectedly improves stability of antibody formulation. The stability of the antibody formulation was measured in terms of degradation and aggregation by Size Exclusion Chromatography (SEC). Applicant has asserted that the use of glutamate instead of citrate reduces the degradation and aggregation of the antibody formulation by 30% and 34%, respectively.

However, the declaration is not sufficient to demonstrate unexpected results of the full breadth of the claimed invention.

The claimed invention is drawn to a stable liquid medical formulation comprising a CD40 antibody, a sorbitol, a polysorbate and a glutamate (as a sole buffer) that has pH 4-6.
The formulation used in the declaration consists of an CD40 antibody, a sorbitol, a polysorbate and a glutamate at pH 5.5.

In the specification of the instant application in p.10-11, the term "stable" is defined as to retain physical, chemical and/or biological activities of the antibody and is desired to have a small ratio

of aggregation by SEC after storage (e.g. 1 month at 40°C, p. 11). The specification of the instant application fails to disclose a certain percentage of aggregation by SEC to further define stability of the antibody formulation.

U.S. Pat. No. 6,875,432, newly cited, states that the term "stable" is defined to have less than 10% preferably less than 5% of aggregation upon storage at various conditions including 2-8°C for 1 year, 25°C for 3 months and 40°C for a month (col. 11, lines 35-50).

Applicant's assertion of reduction of degradation and aggregation (30% and 34%, respectively) of the antibody formulation in glutamate buffer is deemed substantial but the actual degradation of the antibody in glutamate is about 2% and little over 3% in citrate after 1 month of storage at 40°C (see p.4 of declaration). Further, the aggregation of the antibody is about 2% in both glutamate and citrate (see initial bar, p. 5 declaration) and 3-4.5% upon light treatment. As disclosed in the '432 patent, the reduction of aggregation and degradation in the glutamate buffer is expected as the ranges are within the prior art defines the stability. Therefore, the declaration is not sufficient to demonstrate the asserted unexpected results.

Further, the claimed antibody formulation and the antibody formulation used in the declaration differ in the scope. The claimed antibody formulation allows other additives while the antibody formulation used in the declaration is limited to the antibody, sorbitol, polysorbate and glutamate.

Note the earlier statement in this section, "the claimed invention is drawn to a stable liquid medical formulation comprising a CD40 antibody, a sorbitol, a polysorbate and a glutamate (as a sole buffer) that has pH 4-6". Given that the term "comprising" is used in the claimed invention, the formulation allows other additives (e.g. pH adjusting agent, stabilizer, etc). In the specification of the instant application in p. 16, the additives have been further defined to differentiate a buffer agent and a pH adjusting agent (see under additives). Therefore, the claimed antibody formulation does not exclude other additives and the claimed antibody formulation is not limited to an antibody, sorbitol, polysorbate and glutamate.

Further, in the specification of the instant application (p. 17 and 18), ascorbic acid has been listed under the buffer agent and the stabilizer. Given that the ascorbic acid is also a stabilizer, the currently amended claim may also include ascorbic acid.

Also, U.S. Pub. 2003/0124119A1, newly cited, discloses that the acetic acid (or acetate) is known to reduce local irritancy and acts as stabilizer in addition to widely known pH adjusting agent. The prior art, U.S. Pat. No. 6,171,586, of record, also includes acetate in the antibody formulation (see claims 1-29).

Applicant's demonstration of unexpected results is not commensurate the scope of the claimed invention. Thus, the declaration is not sufficient to demonstrate unexpected results of the full breadth of the claimed invention.

4. In light of Applicants' amendments to the claims filed on 11/9/09, the following rejection remains.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 2, 4, 7, 9-14, 18 and 21 stand rejected under 35 U.S.C. 103 as being unpatentable over U.S. Pat. No. 6,171,586B1, of record, in view of U.S. Pat. No. 5,677,165, of record, for the reasons set forth in the office action mailed on 4/20/09.

The '586 patent teaches a stable aqueous pharmaceutical antibody formulation comprising an antibody in a acetate buffer at pH 4.5-6 (col. 6, lines 61-col. 7, lines 3, col. 5, lines 50-65, claims 1-29). The '586 patent teaches the formulation prefers no addition of NaCl (col. 22, lines 31-35), but prefers addition of sorbitol as an isotonizing agent (e.g. tonifier, col. 6, line 52) and addition of polysorbate 80 as a surfactant (col. 22, lines 49-55). The referenced term "pharmaceutical" is interpreted to mean the claimed "medical".

Moreover, the '586 patent teaches the antibody is humanized, monoclonal antibody or chimeric antibody (col. 13-17). Claims 13-14 are included in this rejection as the purification methods of said antibody differentiate IgG1-4 and the resultant antibodies are IgG1-4 (col. 21, lines 41-65). The '586 patent further teaches the use of EDTA as a stabilizer (col. 23, lines 11).

The '586 patent teaches that the antibody formulation comprising a buffer, surfactant and stabilizer improves stability (col. 1, lines 15-40, col. 5-6, overlapping paragraph) and this formulation works for antibody formulation of various antigen targets (col. 10, lines 5- col. 11, lines 14).

Furthermore, the '586 patent teaches that the buffer concentration is 1-50mM (col. 22, line 26), the concentration of the antibody is 2mg/ml to 10 mg/ml (col. 22, line 16), the concentration of surfactant (polysorbate 80) is 0.01% (col. 22, lines 49-60) and the osmotic pressure is between 250mOsm and 350mOsm (col. 6, lines 32-36). The percent concentration of 1g/100ml is 1%, the 0.01% of polysorbate 80 is equivalent to 0.1mg/ml.

The disclosure of the '586 patent differs from the claimed invention in that it does not teach use of glutamate and the use of CD-40 antibody as in claim 1 of the instant application.

The '165 patent teaches the antibody specific to CD40 and addition of glutamate in other buffer system to minimize pH change (col. 7, lines 41-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add or to substitute glutamate and employ CD40 antibody as taught by the '165 patent to the antibody formulation taught by the '586 patent.

It is prima facie obvious to combine two components each of which is taught by prior art to be useful for the same purpose (e.g. adjusting pH) in order to form the third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ1069, CCPA 1980. See MPEP 2144.06.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the substitution of the CD-40 antibody to the antibody formulation taught by the '586 patent improves overall stability of the antibody and the addition of glutamate into other buffer system minimizes the pH change of the antibody solution.

From the teachings of references, it would have been obvious to one of ordinary skill in art to combine the teachings of the references and there would have been a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary in the art at the time of invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 11/9/09 have been fully considered but they are not persuasive.

Applicant has asserted that the declaration of Eiji Sawa has demonstrated the unexpected results by using glutamate instead of citrate and thus the combination of the references is not obvious.

In light of the discussion above in section 3 of this office action, the declaration of Eiji Sawa is not sufficient to demonstrate the unexpected results of the full breadth of the claimed invention.

7. The following new ground of rejection is necessitated by Applicant's amendments filed on 11/9/09.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out this invention.

9. Claims 1, 2, 4, 7, 9-14, 18 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The specification or the original claims as filed does not provide a written description the phrase "glutamate as sole buffer". Applicant has failed to provide the support for the phrase. Even though the specification of the instant application in p. 17 discloses that the glutamate is most preferred among other organic acids, there is no support for the glutamate is the "only buffer". The instant claims now recite a limitation which was not clearly disclosed in the specification as filed, and now changes the scope of instant disclosure as filed.

Such limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C.112.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to YUNSOO KIM whose telephone number is (571)272-3176. The examiner can normally be reached on M-F,9-5. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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